## REMARKS

Claims 1, 71 to 73, and 76 to 79 are pending in this patent application. No claims have been amended, canceled, or added, herein. Applicants respectfully request reconsideration of the rejections of record in view of the following remarks.

### Alleged Obviousness

Claims 1, 71 to 73, and 76 to 79 have been rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by Wyatt, *et al.*, *Nucleic Acids Res.*, 1989, 17, 7833-7842 ("the Wyatt article"), Monia, *et al.*, *J. Biol. Chem.*, 1993, 268, 14514-14522 ("the Monia article"), Manche, et al., *Mol. Cell Biol.*, 1992, 12, 5238-5248 ("the Manche article"), and U.S. Patent Number 5,801,154 ("the Baracchini patent"). Applicants respectfully request reconsideration and withdrawal of this rejection because, as discussed repeatedly during prosecution of this application, those of ordinary skill in the art would have had no reason to design and produce the claimed oligomeric compounds at the time of the invention.

This application has been pending since November, 2003. In the ensuing seven years, claims in this and related applications have been serially rejected under 35 U.S.C. §§ 112, 101, 102, and most recently, 103. Applicants have repeatedly replied at great expense to office action after office action, overcoming one set of rejections, only to be confronted with a new set. In response to the previous rejections under 35 U.S.C. § 103, applicants provided a Declaration from Dr. David Corey, a noted scientist who has been active in the field since the time of the original filing. That Declaration sets forth in detail the factual basis for why one of skill in the art would not have found the claimed oligomeric compounds obvious. The Office dismissed this declaration, however, simply labeling it non-persuasive. Hoping at long last to resolve this application, applicants then appealed to the Board of Patent Appeals and Interferences and submitted a request for a pre-appeal brief conference that also sets forth in detail why the claimed oligomeric compounds would not have been obvious at the time of the invention. After the notice of appeal and request for a pre-appeal brief conference were filed, rather than allowing the claims, or even allowing the application to proceed to appeal to finally resolve the outstanding issues, the Office instead re-opened prosecution, with allegedly "new" grounds for

once again rejecting the claims as obvious. The present rejections rely on several references already addressed by the applicants and discussed by Dr. Corey. Those previously discussed references are now combined with new, largely duplicative references, not previously cited throughout the long prosecution history of this application. As explained below, these "new" rejections fail for the same fundamental reason as the appealed rejections: the Office has still not provided a reason why one of skill in the art would have made the claimed compounds prior to invention by the applicants.

Because obviousness must be analyzed as of the time that an invention was made, it is imperative that the Patent Office avoid resorting to hindsight when assessing obviousness.[1] To avoid relying on hindsight, the Office must therefore demonstrate that the cited prior art reference or combination of references teaches or suggests all the limitations of the claims.[2] And rejections under § 103 must also be supported by "a *reason* that would have prompted a person of ordinary skill in the relevant field to combine the elements *in the way the claimed new invention does*."[3]

Those of ordinary skill in the art would not have had any reason to design and produce the claimed oligomeric compounds before applicants' invention in view of the description provided in the cited references and the state of the art at that time. Specifically, those of ordinary skill in the art would not have had a reason at the time of the invention to produce duplexes of fully complementary oligomeric compounds consisting of 17 to 25 linked nucleosides in which each strand of the duplexes comprises at least one modified nucleoside comprising a sugar surrogate, in view of the description provided in the cited references.

In this regard, the Wyatt article does not describe or suggest fully complementary oligomeric compounds consisting of 17 to 25 linked nucleosides in which each strand of the duplex comprises at least one modified nucleoside comprising a sugar surrogate, and nothing in the Wyatt article would have prompted those of ordinary skill in the art to produce such

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[1] See e.g., *KSR Int'l Co. v. Teleflex*, 127 S.Ct. 1727, 1742 (2007) (warning against "the distortion caused by hindsight bias . . . and arguments reliant on *ex post* reasoning."); 35 U.S.C. § 103 (requiring determination of whether an invention "would have been obvious at the time the invention was made.").
[2] *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974); *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).
[3] *Id.* (emphasis added).

duplexes. Rather, the Wyatt article describes duplexes of complementary 14-mer oligoribonucleotides, and also describes 14-mer oligoribonucleotide duplexes in which one or two 2'-deoxyribonucleotides were substituted for the ribonucleotides in one or both of the strands. The duplexes were used in *in vitro* experiments aimed towards determining the structural requirements of RNase $V_1$. In these experiments, the oligoribonucleotide duplexes and deoxy-substituted duplexes were incubated *in vitro* with the RNase $V_1$ and buffer, and the article reports that the deoxy substitutions reduced cleavage by RNase $V_1$. Significantly, no other ribonucleases were present during the RNase $V_1$ reactions.

The Wyatt article also describes experiments designed to determine the structural requirements for *E. coli* RNase H that utilized 14-mer oligoribonucleotides with or without one or two 2'-deoxyribonucleotide substitutions hybridized to complementary 17-mer deoxyoligoribonucleotides or hybridized to complementary 17-mer oligoribonucleotides having one or two 2'-deoxyribonucleotide substitutions. In the RNase H reactions, the substrates were incubated *in vitro* with RNase H and buffer, and the reactions did not contain any other ribonucleases. The article indicates that deoxy substitutions in the RNA strand of the RNA:DNA hybrids inhibited cleavage by RNase H. Significantly, the Wyatt article provides no teaching or suggestion that would have prompted those skilled in the art to incorporate at least one modified nucleoside comprising a sugar surrogate into both strands of a duplex of oligomeric compounds. Nothing about the design or nature of the experiments described in the Wyatt article would have provided a reason to introduce modified nucleosides comprising sugar surrogates into *both* strands of an oligomeric compound duplex.

The remaining references fail to supply this missing teaching or suggestion, and thus fail to compensate for the deficiencies of the Wyatt article. The Monia article fails to provide any description that would have prompted those of ordinary skill in the art to incorporate at least one modified nucleoside comprising a sugar surrogate into both strands of an oligomeric compound duplex. Instead, the Monia article describes 17-mer oligonucleotides having a central gap region

of 2'-deoxynucleotides and having 5' and 3' wing regions of 2'-OMe substituted nucleotides.[4] These gapmers were hybridized to the following complementary RNAs:

1. A synthetic, end-labeled 25-mer RNA corresponding to Ha-*ras* RNA. The resulting duplex was used in *in vitro* melting experiments;

2. A 47-mer Ha-*ras* RNA hairpin. The resulting duplex was used in *in vitro* RNase activation experiments; and

3. Full-length Ha-*ras* mRNA, after introduction of the gapmer into HeLa cells that had been transfected with an Ha-*ras* expression plasmid, to determine the antisense activity of the gapmer.

The Monia article also describes hybridization of 11-mer, 13-mer, or 15-mer 2'-OMe gapmers to end-labeled 25-mer RNAs corresponding to Ha-*ras* RNA. The resulting duplexes was used in *in vitro* melting experiments.[5]

Finally, the Monia article describes melting experiments that utilized 17-mer gapmers having a central, 2'-deoxy region and 5' and 3' wing regions of either 2'-deoxy, 2'-O-pentyl, 2'-O-propyl, 2'-O-methyl, or 2'-fluoro groups hybridized to 25-mer RNAs corresponding to Ha-*ras* RNA.[6] These gapmers were also introduced into HeLa cells that had been transfected with an Ha-*ras* expression plasmid to determine their antisense activity against full-length Ha-*ras* mRNA.

Significantly, the Monia article contains no teaching or description that would have prompted those of ordinary skill in the art to incorporate at least one modified nucleoside comprising a sugar surrogate into *both* strands of an oligomeric compound duplex. The *in vitro* melting and RNase activation experiments described in the Monia article utilized duplexes in which only one strand contained chemical modifications, and there would have been no reason to utilize substrates having chemical modifications in both strands in such experiments. Furthermore, in the experiments in which the antisense activity of the single-stranded gapmers was analyzed, *duplexes* were not introduced into HeLa cells, but, rather, single-stranded gapmers

[4] Figure 1
[5] Figure 8A.
[6] Table II.

were introduced, and their activity against unmodified, full-length mRNA target was determined. Accordingly, nothing about the design or objective of the experiments described in the Monia article would have prompted those of ordinary skill in the art to incorporate chemical modifications into both strands of a duplex of oligomeric compounds, much less incorporate at least one modified nucleoside comprising a sugar surrogate into both strands of a duplex, as claimed.

Similarly, as discussed at length previously during prosecution of this application and as explained by Dr. Corey in his declaration,[7] the Manche article also fails to provide such a teaching or suggestion. Instead, the Manche article describes short RNA duplexes that were used as substrates in experiments designed to elucidate the mechanism of activation of interferon-induced protein kinase DAI. Specifically, the experiments involved binding DAI to RNA duplexes of 15, 23, 34, 40, 55, 67, 85, or 104 nucleotides *in vitro*.[8] The RNA duplexes were not chemically modified, and as pointed out by Dr. Corey in his declaration,[9] nothing about the nature or aim of the experiments described in the Manche article provides any reason that would have prompted those of ordinary skill in the art to produce chemically modified RNA duplexes, much less duplexes having at least one modified nucleoside comprising a sugar surrogate in both strands, as claimed.

Finally, as discussed by Dr. Corey in his declaration,[10] the Baracchini patent also fails to provide such a reason. Instead, the Baracchini patent describes single-stranded antisense deoxynucleotides targeted against mRNA encoding multidrug resistance associate protein (MRP). Although the Baracchini patent describes chemical modification of antisense deoxynucleotides, as explained by Dr. Corey,[11] the patent does not describe or suggest any reason to introduce chemical modifications into *duplexes* of oligomeric compounds consisting of 17 to 25 linked nucleosides.

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[7] Declaration of Dr. David Corey filed August 19, 2009, paragraphs 16 to 19.
[8] Figure 1A.
[9] *Id.*
[10] Declaration of Dr. David Corey filed August 19, 2009, paragraphs 20 to 24.
[11] *Id.*

Those of ordinary skill in the art therefore would have had no reason to produce duplexes of fully complementary oligomeric compounds consisting of 17 to 25 linked nucleosides in which each strand of the duplexes comprises at least one modified nucleoside comprising a sugar surrogate before applicants' invention in view of the description provided in the cited references, when considered in combination in view of the state of the art at that time. The claimed oligomeric compounds therefore would not have been obvious before applicants' invention.

The Office asserts, however, that "the person of ordinary skill in the art would have reason to incorporate 2'-sugar groups into the duplex because these references teach that nucleolytic degradation is a problem for nucleic acids and that stabilization of a duplex with modified nucleotides provide resistance to nucleases."[12] Contrary to the Office's assertion, those of ordinary skill would *not* have had a reason to incorporate chemical modifications, such as sugar surrogates, into *both* strands of an oligomeric compound duplex at the time of the invention because the experiments described in the cited references do not involve conditions in which undesired nucleolytic degradation of such duplexes could have occurred. In the *in vitro* experiments described in the references, such as the RNase H and RNase $V_1$ digestion experiments, in accordance with the experimental designs used, undesired nucleases were not present during the reactions that could have potentially degraded the substrates. As discussed above, only the RNase H and RNase $V_1$ endonucleases were present in the reaction mixtures, and no other enzymes were present. Furthermore, in the experiments in which nucleic acids were introduced into cells or were treated with cellular extracts, *single-stranded* oligonucleotides targeted against full-length mRNAs were used in such experiments, and double-stranded duplexes were not utilized. None of the references therefore describes experiments in which double-stranded nucleic acids were introduced into an environment in which undesired nucleolytic degradation of the duplexes could have occurred. Accordingly, contrary to the Office' assertion, the cited references fail to provide any reason that would have prompted those of ordinary skill in the art to protect both strands of a duplex of oligomeric compounds of the length claimed against nucleolytic degradation by introducing chemical modifications into both strands of such duplexes. Dr. Corey explained that such compounds would not have been

[12] Office action dated June 22, 2010, page 6.

particularly suitable for the research described in the previously cited references, including the Manche article and the Baracchini patent. Likewise, there would have been no reason why one skilled in the art would have used such compounds for the research described in the additional, newly-cited references. Because none of the cited reference, nor all of them combined, describe research for which one skilled in the art would have had a reason to make the claimed oligomeric compounds, such compounds would not have been obvious at the time of the invention.

By submitting this reply, applicants are yet again responding to the assertions made in the official action in effort to resolve all of the outstanding issues for this application so as to advance it to allowance. Applicants again, accordingly, respectfully request withdrawal of the rejection for alleged obviousness.

## Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the official action of record. Accordingly, an early and favorable action is respectfully requested.

Respectfully submitted,

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